

**REMARKS**

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claim 1 has been amended to re-insert the proviso language previously deleted from the claim. Claim 1 thus again now recites that "when A is a benzene ring and R<sup>1</sup> is an amino group, R<sup>2</sup> and R<sup>3</sup> are not a hydrogen atom at the same time." No new matter is added by this amendment. This language finds support in the application as originally filed.

For example, many of the original Examples show compounds as now claimed, wherein when A is a benzene ring and R<sup>1</sup> is an amino group, R<sup>2</sup> and R<sup>3</sup> are not a hydrogen atom at the same time. More specifically, Examples 9, 10, 17, 18, 23, 26, 27, 30 and 32 exemplify such compounds as now claimed. The compounds of these Examples provide written description support for the claim language.

The new matter prohibition is closely related to the adequate disclosure requirements of §112(1). See, *Pennwalt Corp. v. Akzona Inc.*, 740 F.2d 1573, 1578, 222 USPQ 833, 836 (Fed. Cir. 1984). Section 112 requires "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same." 35 U.S.C. §112. The written description requirement together with the new matter prohibition of 35 U.S.C. §132 "serve to ensure that the patent application was in full possession of the claimed subject matter on the application filing date." *TurboCare Division of Demag Delaval Turbomachinery Corp. v. General Electric Co.*, 264 F.3d 111, 60 USPQ2d 1017 (Fed. Cir. 2001). The purpose of the written description requirement is to "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention," as now claimed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). As stated in *In re Kaslow*, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983):

The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. *In re*

*Edwards*, 558 [568] F.2d 1349, 196 USPQ 465 (CCPA 1978); *In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979).

See also, *In re Wilder*, 736 F.2d 1516, 222 USPQ 369 (Fed. Cir. 1984).

Legal precedent shows that *ipsis verbis* support is not necessary for a claimed invention:

The invention claimed in the later application does not have to be described in the prior application in *ipsis verbis* in order to satisfy the description requirement of section 112 . . . . However, claims with no explicit disclosure must find inherent support in the prior application, *Pingree v. Hull*, 518 F.2d 624, 186 USPQ 248 (CCPA 1975); and one skilled in the art, following the teaching of the prior application must be able to produce the subject matter of the later claims. *In re Magerlein*, 346 F.2d 609, 612, 145 USPQ 683, 685 (CCPA 1975); *In re Nathan*, 328 F.2d 1005, 1008-09, 140 USPQ 601, 604 (CCPA 1964).

*Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 USPQ 177 (Fed. Cir. 1985). See also, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996); *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000).

In view of the above, it is respectfully submitted that claim 1 as amended is supported by the instant application.

Claims 26-31 have also been added. Support for these claims may be found at the very least in original claim 1 and in Examples 9, 10, 17, 18, 23, 26, 27, 30 and 32. No new matter is added by these claims.

Claims 1-6 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Fukami et al. This rejection is respectfully traversed.

Column 52, Example 148, is cited as teaching the same compound as claimed in formula (1) of the instant invention, when X is chloro at position 7, A is phenyl, R<sup>1</sup> is amino at position 4, and R<sup>2</sup> and R<sup>3</sup> are hydrogen. This compound of Fukami et al is not included within the scope of the claims in view of the proviso language. Claims 1-6 thus are not anticipated by the reference.

Nor would the claimed compounds be obvious in view of Example 148 of Fukami et al. Unexpected results are achieved by the claimed compounds over the 4-aminobenzenesulfonyl of Fukami et al. A signed Declaration of Dr. Muto was submitted with the Supplemental Reply on April 18, 2003. This Declaration evidences the unexpected and improved results achieved by the instantly claimed compounds.

In the Declaration, the solubilities of compounds described in Examples 13, 17 and 18 of the instant application and of the compound of Example 148 of Fukami et al were measured. The compounds of Examples 13, 17 and 18 are specifically included in new claim 26. The results are given in Table I of the Declaration. As can be seen therein, the solubilities of the compounds of the instant invention are surprisingly significantly higher than that of Example 148 of Fukami et al.

For example, the solubilities in water of the compounds encompassed by the instant claims, for example, the compounds described in Examples 13, 17 and 18 of the present application, are remarkably or unexpectedly higher than that of Example 148 of US '631. The results can be summarized as follows:

Table I

<u>Sample Compound</u>	<u>Solubility in Water (<math>\mu\text{g/mL}</math>)</u>
Example 13	88.5
Example 17	78.9
Example 18	98.8
Example 148 of US '631	6.9

Namely, when compared with the cited compound of example 148 having 4-aminobenzenesulfonyl, the compounds having  $\text{NH}_2$  for  $\text{R}^1$  and the substituents for  $\text{R}^2$  and  $\text{R}^3$  (i.e., the present compounds 17 and 18) and the compound having  $\text{NHCOR}$  for  $\text{R}^1$  (i.e., the present compound 13) have unexpectedly high solubilities in water. Since one skilled in the art would have expected the position isomers to have the same properties, the properties of the claimed compounds are truly unexpected.

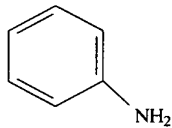
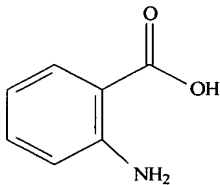
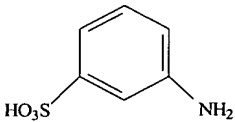
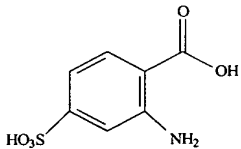
As is well-known in the art, the oral absorbability in the oral administration depends upon the dissolving rate of the drug and the dissolving rate in the case of oral administration generally depends upon the solubility in water of the drug.

Thus, the solubilities of the present compounds 13, 17 and 18 are remarkably higher than that of the cited compound 148. Because of the difference in solubilities, when compared with the cited compound of example 148, the compounds of the instant invention encompassed by claims 1-6 are

expected to have a higher oral absorbability and bioavailability than those of the '631 Patent. The instantly claimed compounds would thus be expected to have a higher effectiveness when orally administered. In addition, in the case of non-oral administration, since drugs should be dissolved in injection solutions, the drugs having a solubility in water are advantageous for non-oral administration as well.

The solubilities of the claimed compounds are more than 11 times higher than that of Example 148 of Fukami et al. Such an increase in solubilities would not be expected prior to the instant application. The assertion that the increase in solubility would have been expected due to the carboxylic acid group is incorrect. It is recognized in the art that the solubilities of compounds with carboxylic acid groups are not necessarily higher, and in fact, may be lower than the solubilities of the corresponding amines.

For example, the solubilities in water of the partial structure of Example 148 of US '631 and the partial structure of Example 17 of the present invention can be summarized from the data in the reference (i.e., Beilstein Handbook of Organic Chemistry), as follows:

Compound	Structure	Solubility (g/L)	Temperature (deg.)	Reference
aniline		3.65	25	Beilstein Handbook of Organic Chemistry, EIII, 12, 217.
anthlanilic acid		3.5	14	Beilstein Handbook of Organic Chemistry, EI, 14, 529.
		5.87	32	Beilstein Handbook of Organic Chemistry, EIII, 14, 879.
3-aminobenzenesulfonic acid		19.5	9	Beilstein Handbook of Organic Chemistry, H 14, 688.
2-amino-4-sulfobenzoic acid		10.5	25	Beilstein Handbook of Organic Chemistry, EI, 14, 770.

(Note) The solubility data was converted to the same unit (g/L) from the data in reference.

As is clear from the above data, the solubilities of compounds after the addition of a COOH group do *not* necessarily increase, and in fact may actually *decrease*. Consequently, one skilled in the art would *not* have expected that the solubility of the claimed compounds would increase, much less that they would be more than 11 times higher than that of Example 148 of Fukami et al. Applicants finding of chymase inhibitor compounds having a remarkably increased solubility and an excellent oral absorbability was, therefore, by no means obvious to those skilled in the art at the time the invention was made. Unexpected results in terms of the 11-fold increase in solubility are thus achieved by the instant invention.

In view of the marked difference in properties of the compound of example 148 of Fukami et al and the compounds of the instant invention, and the unexpected results achieved by the instant invention, the claims of the instant invention would not be obvious in view of Fukami et al.

Claim 25 has been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fukami et al. This rejection is now moot in view of the deletion of claim 25. Withdrawal of the rejection is respectfully requested and believed to be in order.

Claim 25 was rejected under 35 U.S.C. §112, first paragraph. This rejection has also been rendered moot by the deletion of the claim. Withdrawal of the rejection is respectfully requested and believed to be in order.

Claims 1-6 and 13-25 have further been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The phrase "unsubstituted or substituted" for the C<sub>1</sub> to C<sub>4</sub> lower alkyl groups in claims 1 and 25 is said to be unclear regarding what is covered and what is not. It is respectfully submitted that this phrase would be sufficiently clear to a person skilled in the art. One skilled in the art would recognize how the C<sub>1</sub> to C<sub>4</sub> lower alkyl groups could be substituted or not. This is sufficient to satisfy §112(2). "A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed." *Amgen Inc., v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), *cert. denied*, 516 U.S. 988 (1991).

Moreover, the claim should not be read in a vacuum. "Whether a claim is invalid for indefiniteness requires a determination whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Morton International, Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (Fed. Cir. 1993), *on remand from*, 508 U.S. 83, 26 USPQ2d 1721 (1993). In the instant case, the phrase would be particularly clear to one skilled in the art upon reading the specification, in particular, at page 7, line 33 - page 8, line 1.

However, to expedite prosecution of the application, the claims have been amended to define the possible substitution of the C<sub>1</sub> to C<sub>4</sub> lower alkyl groups, in accordance with the preferred embodiments recited in the specification.

In addition, the phrase "prevention or" has been deleted from claims 14-17.

In view of the above, withdrawal of the rejection of the claims under §112(2) is respectfully requested and believed to be in order.

In view of the above, all of the pending claims are believed to now be in condition for allowance. Further and favorable action by the Patent Office in the form of a Notice of Allowance is thus respectfully requested and believed to be in order.

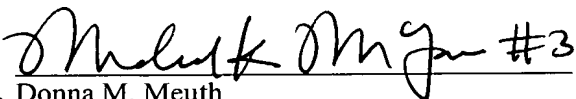
In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (650) 622-2360 so that prosecution of the application may be expedited.

Respectfully submitted,

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